

Antitrombotika-kontroverze:

*Pacient dostal lékový stent:
DAPT na 6 měsíců je dostatečná!*

P. Červinka

Krajská zdravotní a.s., Masarykova nemocnice v Ústí nad Labem o.z
a UJEP Ústí nad Labem



➤ DAPT na 6 měsíců je dostatečná!



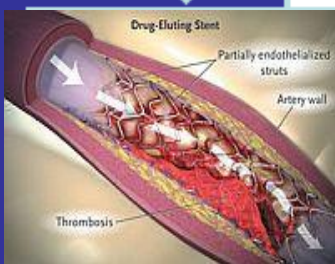
➤ DAPT na 6 měsíců je dostatečná!

„Současné znalosti hovoří pro individualizaci trvání DAPT na základě bedlivého posouzení ischemického a krvácivého rizika a přání nemocného“

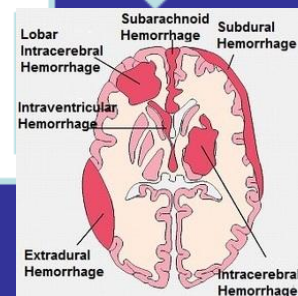


➤ DAPT na 6 měsíců je dostatečná!

Thrombosis



Bleeding



“Bleeding is the Cost of Improved Antithrombotic Efficacy” ???



➤ DAPT na 6 měsíců je dostatečná!

▪ Klasifikace krvácení

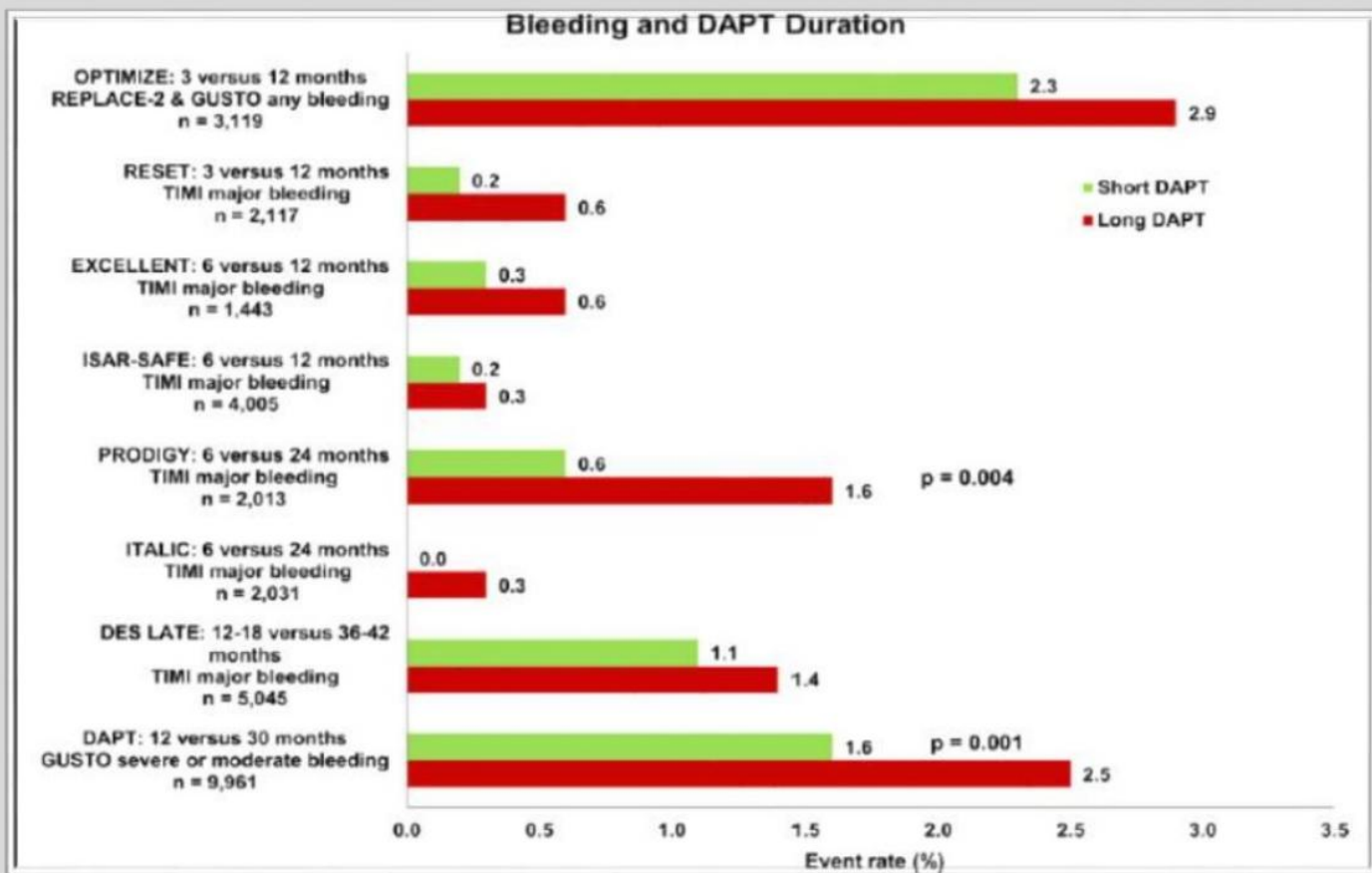
Table 1. BARC Definitions

Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek treatment
Type 2	Any clinically overt sign of hemorrhage that “is actionable” and requires diagnostic studies, hospitalization, or treatment by a health care professional
Type 3	<p>a. Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed); transfusion with overt bleeding</p> <p>b. Overt bleeding plus hemoglobin drop < 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents</p> <p>c. Intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision</p>
Type 4	CABG-related bleeding within 48 hours
Type 5	<p>a. Probable fatal bleeding</p> <p>b. Definite fatal bleeding (overt or autopsy or imaging confirmation)</p>

TIMI Bleeding Classification	
Major	Intracranial haemorrhage or clinically overt bleeding (including imaging) ≥ 5 g/dL decrease in the haemoglobin concentration
Minor	Clinically overt bleeding (including imaging) with 3 to < 5 g/dL decrease in the haemoglobin concentration
Minimal	Clinically overt bleeding (including imaging) with a < 3 g/dL decrease in the haemoglobin concentration
GUSTO Bleeding Classification	
Severe or life threatening	Either intracranial haemorrhage or bleeding that causes haemodynamic compromise and requires intervention
Moderate	Bleeding that requires blood transfusion but does not result in haemodynamic compromise
Mild	Bleeding that does not meet criteria for either severe or moderate bleeding

➤ DAPT na 6 měsíců je dostatečná!

▪ Krvácení a DAPT



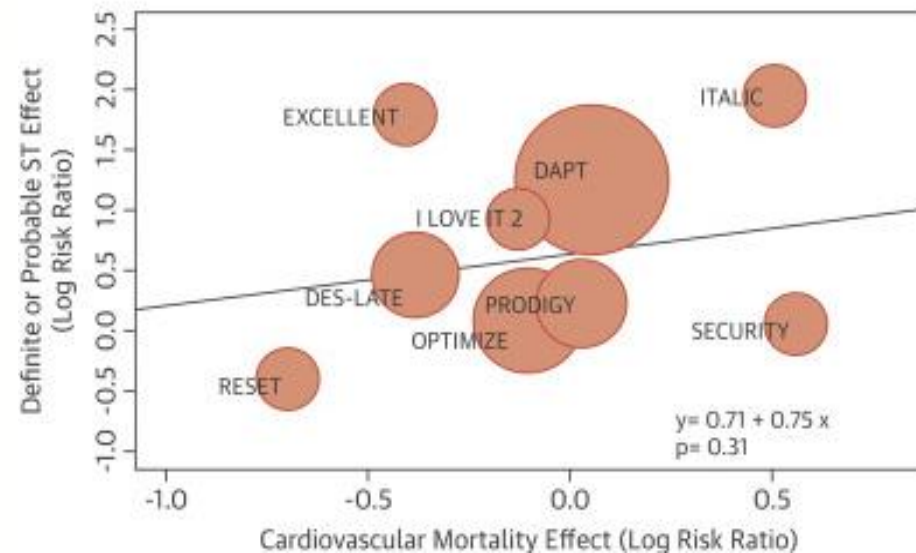
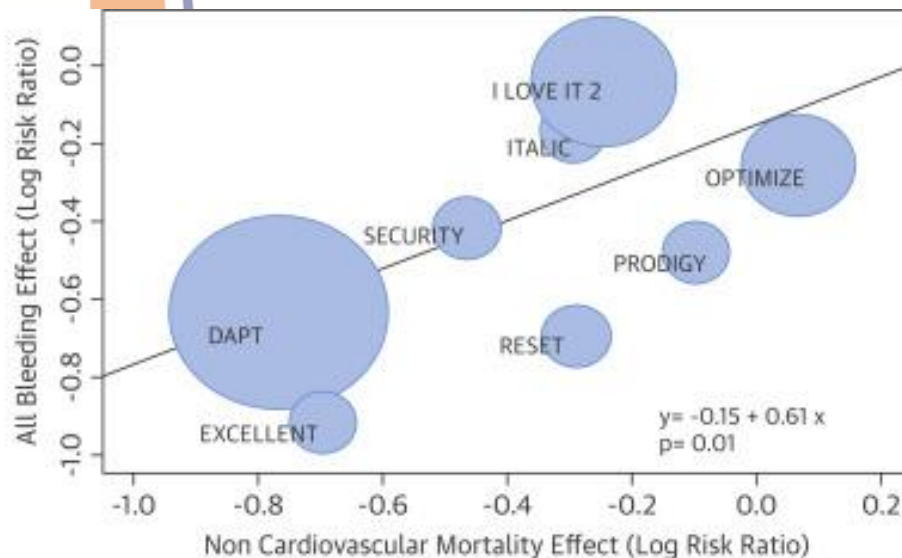
Rates of bleeding are consistently higher for prolonged DAPT, reaching statistical significance in some studies

European Heart Journal (2015) 36, 1207–1211

➤ DAPT na 6 měsíců je dostatečná!

- **Meta-Analyses of Dual Antiplatelet Therapy Following Drug-Eluting Stent Implantation : Do Bleeding and Stent Thrombosis Weigh Similar on Mortality?**

Association Between Log-Transformed Risk of All Bleeding and ST With Noncardiovascular and Cardiovascular Mortality, Respectively
The size of each circle represents the precision of each estimate ...



In conclusion, in drug-eluting stent trials of DAPT duration, bleeding seems to be significantly associated with noncardiovascular mortality, whereas ST does not seem to be significantly associated with cardiovascular mortality. Therefore, DAPT prolongation over current recommendations should only be undertaken after careful consideration of the benefit-risk balance.

➤ DAPT na 6 měsíců je dostatečná!

- ***Klinické a procedurální charakteristiky spojené se zvýšeným ischemickým rizikem nebo krvácením***

Increased Ischemic Risk/Risk of Stent Thrombosis (may favor longer-duration DAPT)

Increased ischemic risk

- Advanced age
- ACS presentation
- Multiple prior MIs
- Extensive CAD
- Diabetes mellitus
- CKD

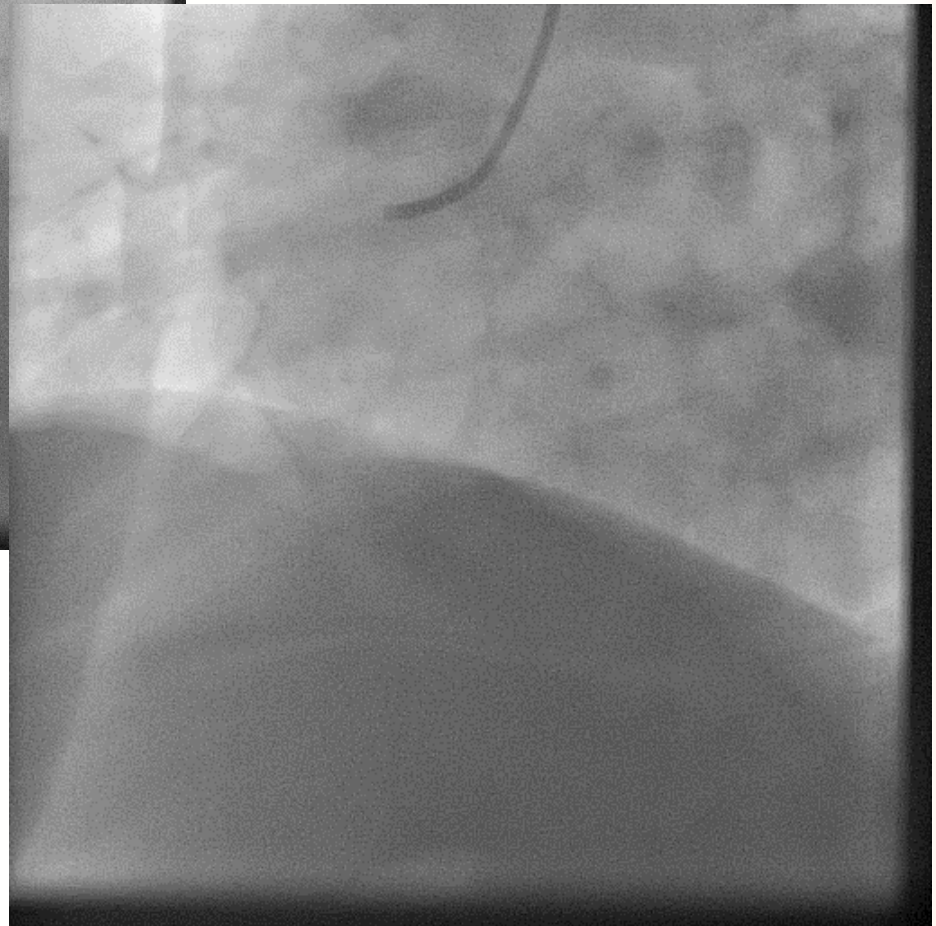
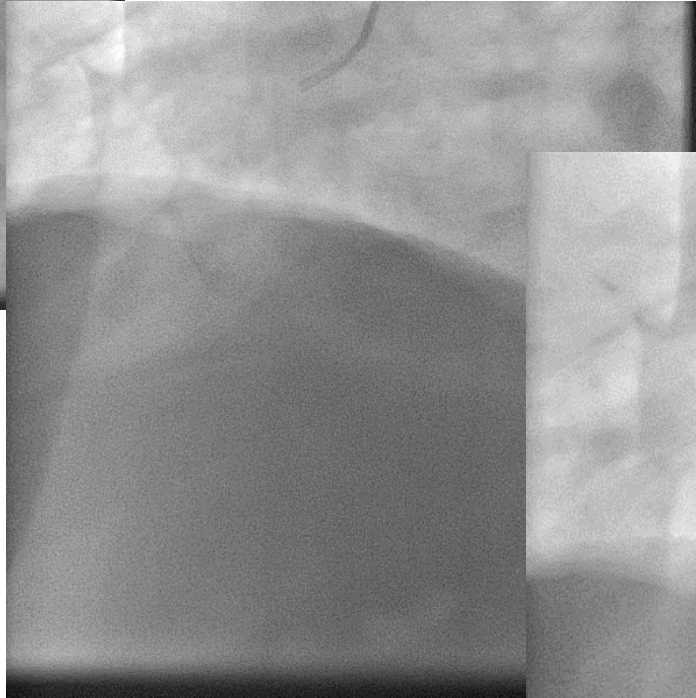
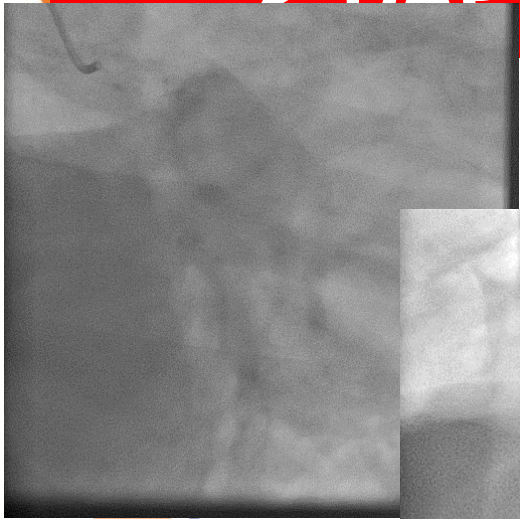
Increased risk of stent thrombosis

- ACS presentation
- Diabetes mellitus
- Left ventricular ejection fraction <40%
- First-generation drug-eluting stent
- Stent undersizing
- Stent underdeployment
- Small stent diameter
- Greater stent length
- Bifurcation stents
- In-stent restenosis

Increased Bleeding Risk (may favor shorter-duration DAPT)

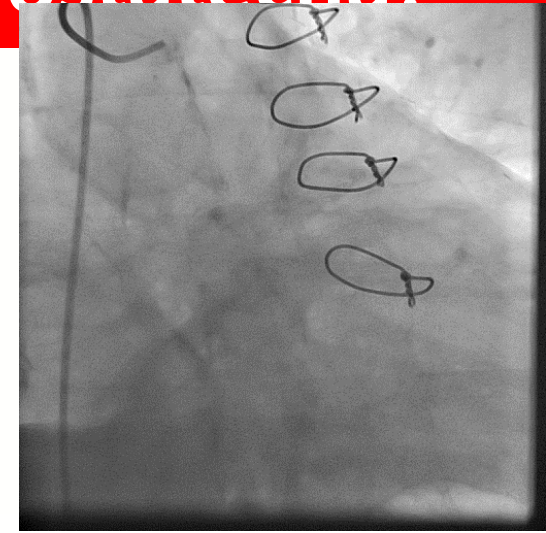
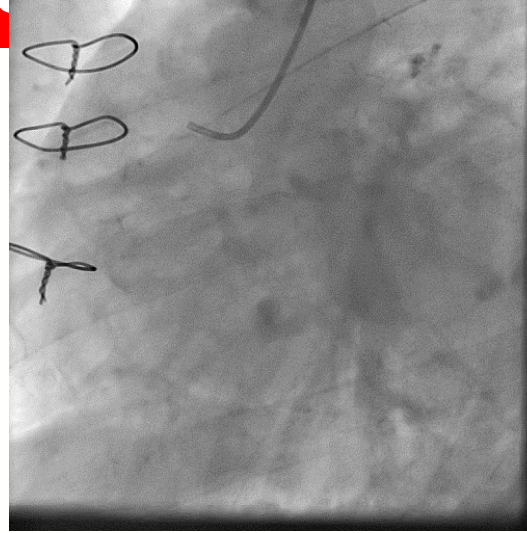
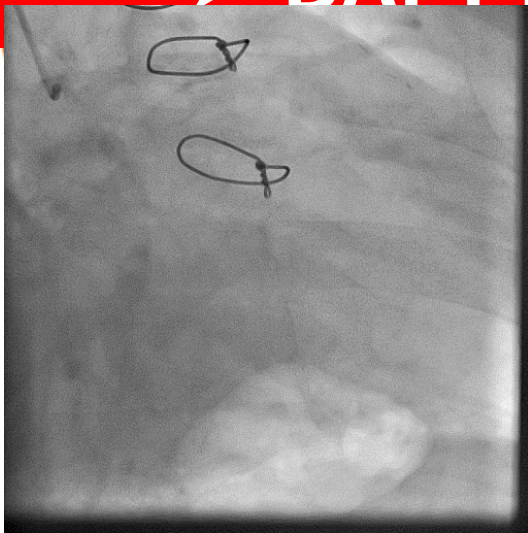
- History of prior bleeding
- Oral anticoagulant therapy
- Female sex
- Advanced age
- Low body weight
- CKD
- Diabetes mellitus
- Anemia
- Chronic steroid or NSAID therapy

➤ DAPT na 6 měsíců je dostatečná!

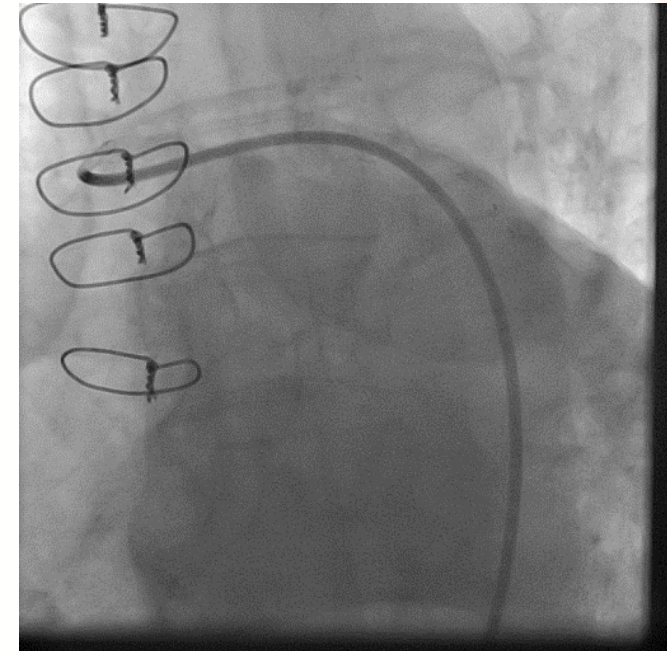


- Muž, 67 let
- kuřák
- Námahová AP II-III KKVK
- 1 VD
- 1 DES 2. generace
(*biodegradabilní polymer, abluminální krytí*)
- **DAPT 3 M**

➤ DAPT na 6 měsíců je dostatečná!



- muž, 74 let
- DM II. typu na inzulínu (CHRI)
- HLP, art. Hypertenze
- ICH tepen DK, PTA bil.
- 2002 LIMA RIA, AKB ad RD a RMS
- po recidiv. IM
- Permanentní Fis na OAK (hematurie při norm. INR)

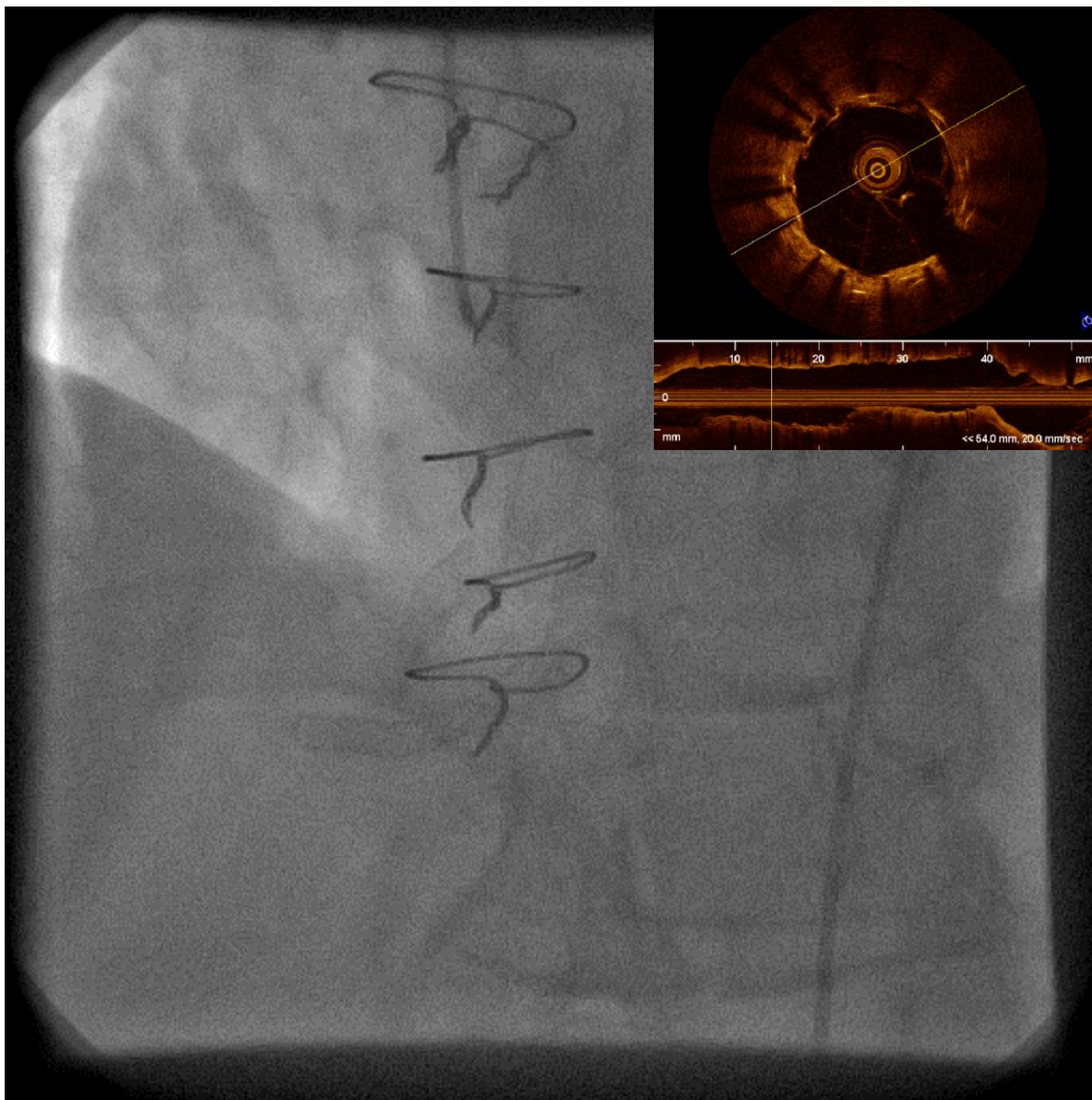


- Nyní NSTEMI
- DES 2. generace (biodegradabilní polymer, abluminální krytí)

▪ **Clpidogrel+warfarin na 6 M, dále pouze W**

➤ DAPT na 6 měsíců je dostatečná!

- žena 73 let, po AKB, DM, K
- po PCI ACD s BMS 2004
- restenóza BMS 12/08;
DES 1. generace
- 7/2010 pozdní trombóza DES
- nepokryté mřížky stentu
- DAPT doživotně



➤ DAPT na 6 měsíců je dostatečná!

- **Doporučení ACC/AHA (2016) a ESC/EACTS (2014)**

Levine, GN, et al.
Focused Update on Duration of Dual Antiplatelet Therapy

2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery

Developed in Collaboration With the American Association for Thoracic Surgery, American Society of Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons

Endorsed by Preventive Cardiovascular Nurses Association and Society for Vascular Surgery



European Heart Journal (2014) 35, 2541–2619
doi:10.1093/eurheartj/ehu278

ESC/EACTS GUIDELINES



2014 ESC/EACTS Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

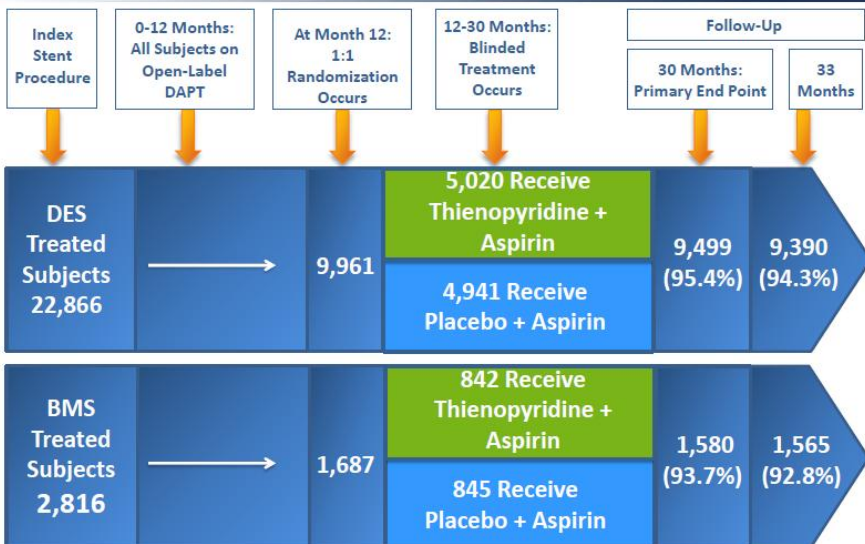
Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI)

Authors/Task Force members: Stephan Windecker* (ESC Chairperson) (Switzerland), Philippe Kolh* (EACTS Chairperson) (Belgium), Fernando Alfonso (Spain), Jean-Philippe Collet (France), Jochen Cremer (Germany), Volkmar Falk (Switzerland), Gerasimos Filippatos (Greece), Christian Hamm (Germany), Stuart J. Head (Netherlands), Peter Jüni (Switzerland), A. Pieter Kappetein (Netherlands), Adnan Kastrati (Germany), Juhani Knuuti (Finland), Ulf Landmesser (Switzerland), Günther Lauffer (Austria), Franz-Josef Neumann (Germany), Dimitrios J. Richter (Greece), Patrick Schauerte (Germany), Miguel Sousa Uva (Portugal), Giulio G. Stefanini (Switzerland), David Paul Taggart (UK), Lucia Torracca (Italy), Marco Valgimigli (Italy), William Wijns (Belgium), and Adam Witkowski (Poland).



➤ DAPT na 6 měsíců je dostatečná!

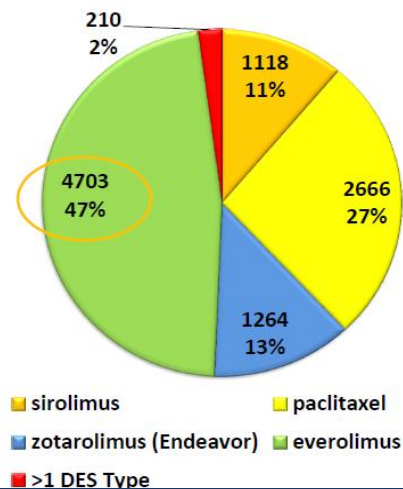
Subject Flow



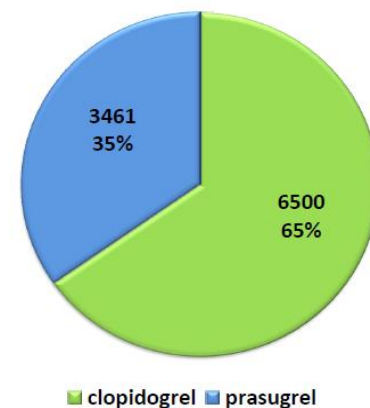
Stent & Drug Types



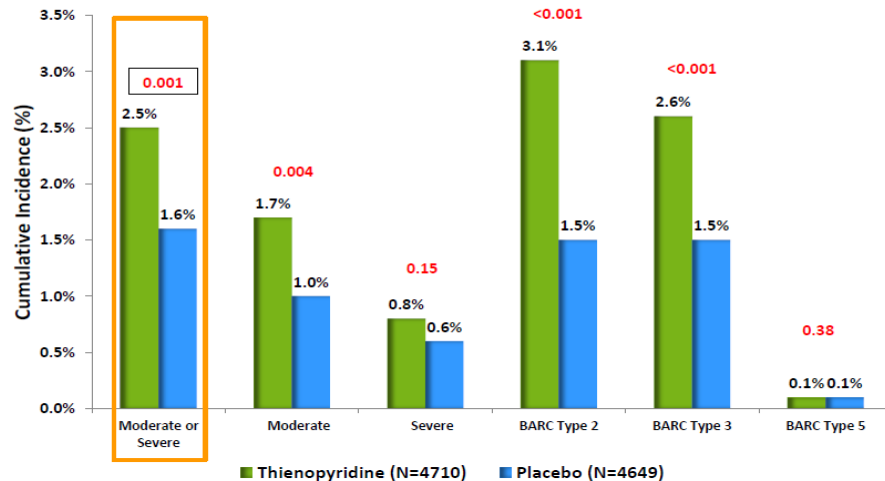
Drug Eluting Stent Type



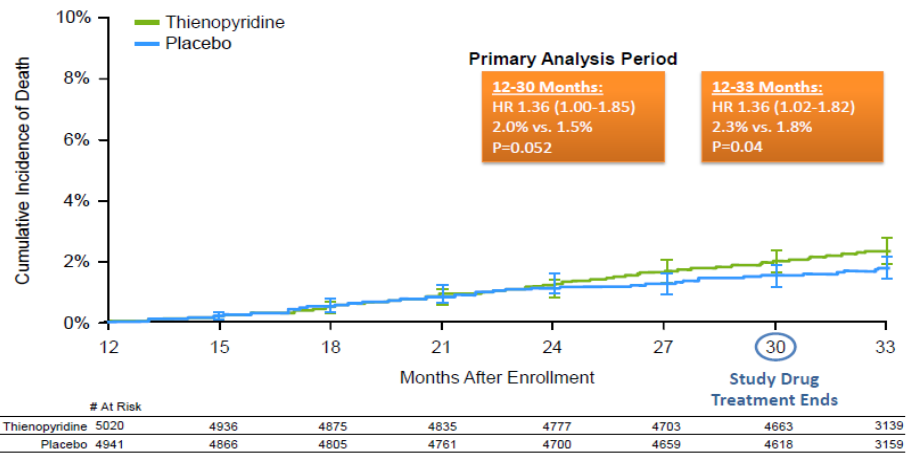
Thienopyridine Type



Primary Safety End Point (Moderate or Severe Bleeding): 12-30 Months



All-Cause Mortality



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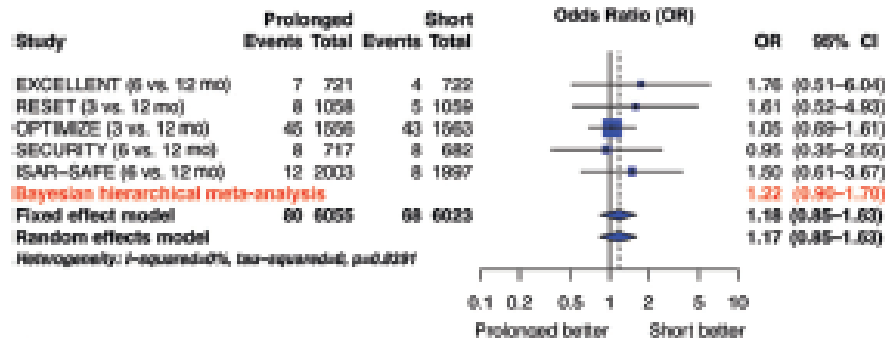
2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease
A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Endpoints After 12 Months Versus Shorter Courses of DAPT After DES Implantation

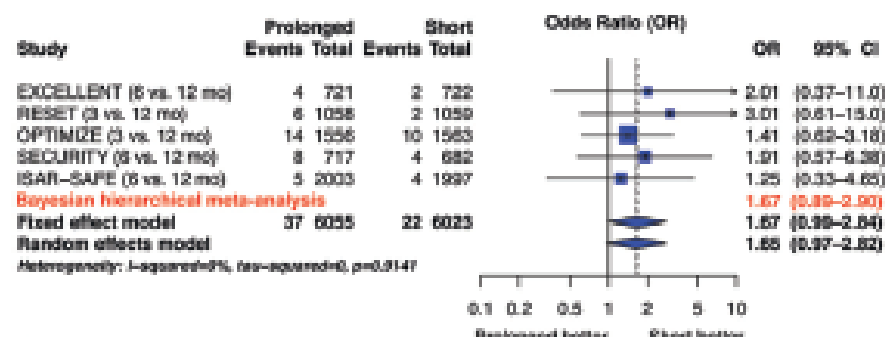
(Stabilní AP i ACS)

3-6 Months vs. 12 Months

A Mortality



B Major hemorrhage

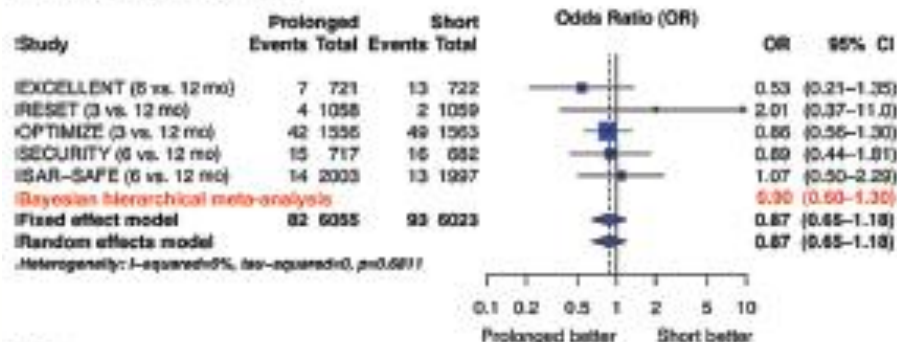


■ **Žádný statistický rozdíl**

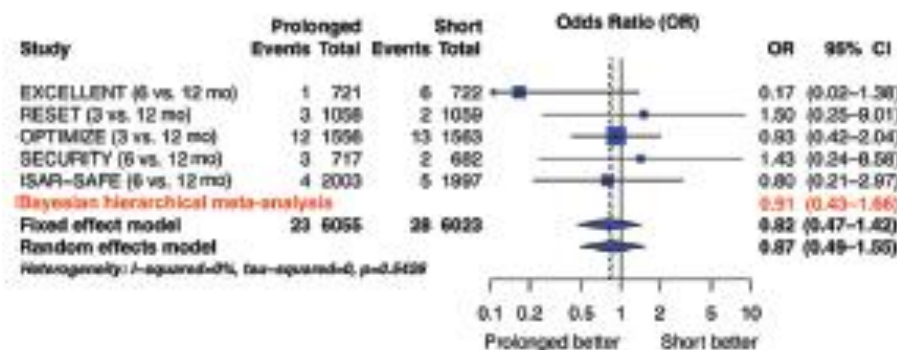
Editorials RESET a SECURITY:

„With newer-generation DES, shorter DAPT duration (3-6M) seems very reasonable to consider and is increasingly used in the art of taking care.“

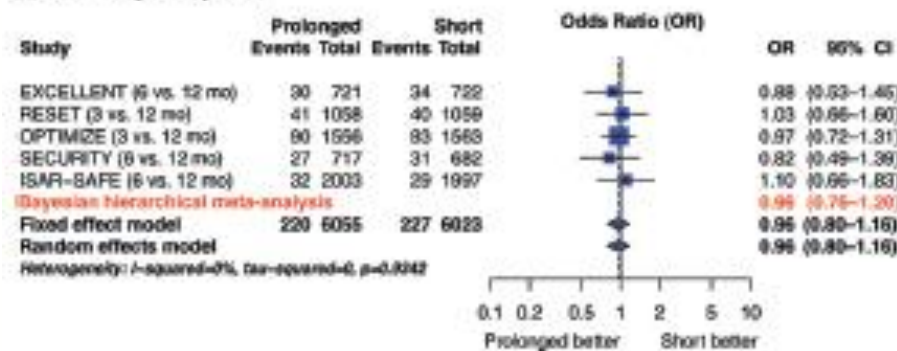
C Myocardial infarction



D Stent thrombosis



E Primary endpoint



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Catheterization and Cardiovascular Interventions 89:178–189 (2017)

CORONARY ARTERY DISEASE

Original Studies

Short-Versus Long-Term Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Women Versus Men: A Sex-Specific Patient-Level Pooled-Analysis of Six Randomized Trials

Fadi J. Sawaya,¹ MD, Marie-Claude Morice,¹ MD, Marco Spaziano,¹ MD, Roxana Mehran,² MD, Romain Didier,³ MD, Andrew Roy,¹ MD, Marco Valgimigli,⁴ MD, PhD, Hyo-Soo Kim,⁵ MD, PhD, Kyung Woo Park,⁵ MD, Myeong-Ki Hong,⁵ MD, PhD, Byeong-Keuk Kim,⁶ MD, PhD, Yangsoo Jang,⁶ MD, PhD, Fausto Feres,⁷ MD, Alexandre Abizaid,⁷ MD, Ricardo A. Costa,⁷ MD, Antonio Colombo,⁸ MD, Alaide Chieffo,⁸ MD, Gennaro Giustino,⁸ MD, Gregg W. Stone,⁹ MD, Deepak L. Bhatt,¹⁰ MD, MPH, Tullio Palmerini,¹¹ MD, and Martine Gilard,^{3*} MD

Background: Whether the efficacy and safety of dual antiplatelet therapy (DAPT) are uniform between sexes is unclear. We sought to compare clinical outcomes between short- (≤6 months) versus long-term (≥1 year) DAPT after drug-eluting stent (DES) placement in women and men. **Methods and Results:** We pooled individual patient data from 6 randomized trials of DAPT (EXCELLENT, OPTIMIZE, PRODIGY, RESET, SECURITY, ITALIC PLUS). The primary outcome was 1-year risk of major adverse cardiac events (MACE). The main secondary outcome was 1-year risk of any bleeding. Out of the 11,473 randomized patients included in the pooled dataset, 3,454 (30%) were females. At 1-year follow-up, women had higher risk of MACE (3.6% vs. 2.8%; $P = 0.01$) but similar risk of bleeding (1.9% vs. 1.6%; $P = 0.16$) as compared with men. Compared with long-term DAPT, short-term DAPT was associated with similar rates of MACE in both women (HR 0.88; 95% CI 0.62–1.25) and men (HR 1.25; 95% CI 0.95–1.6; P interaction = 0.08). At 1-year follow-up, short-term DAPT was associated with lower rates of bleeding as compared with long-term DAPT in both women (HR 0.84; 95% CI 0.51–1.37) and men (HR 0.58; 95% CI 0.40–0.84; P -interaction = 0.25). The presence of MVD was associated with higher MACE rates in the short-term DAPT group in women (HR: 1.16; CI 0.60–2.23) and men (HR: 2.29; CI 1.22–4.29; P interaction = 0.25). **Conclusions:** Short-term DAPT is associated with similar rates of MACE but lower risk of bleeding when as compared with prolonged DAPT. There was no significant difference between sexes in the population studied. © 2016 Wiley Periodicals, Inc.

Key words: dual antiplatelet therapy duration; major adverse cardiac events; drug-eluting stents; women

Study	HR (95% CI)	Weight (%)	Events, Group 1	Events, Group 2
ARCTIC Intervention	0.4 (0.70, 1.60)	36.40	20/4941	22/2020
DAPT	0.68 (0.38, 1.23)	15.03	19/2514	28/2531
DES LATE	0.7 (0.11, 3.88)	1.68	2/722	3/721
EXCELLENT	0.7 (0.40, 1.37)	2.03	5/512	3/510
ISAR SAFE	0.9 (0.56, 1.46)	21.79	24/1583	20/1550
ITALIC	0.82 (0.53, 1.58)	18.14	25/701	27/700
OPTIMIZE	0.9 (0.91, 2.73)	1.86	2/1099	4/1056
PRODIGY	0.44 (0.41, 6.59)	2.81	5/682	3/717
RESET	0.82 (0.73, 1.17)	100.00	128/13144	100/13263
SECURITY	0.83 (0.73, 1.17)	100.00		

Study	HR (95% CI)	Weight (%)	Events, Group 1	Events, Group 2
ARCTIC Intervention	0.47 (0.29, 0.76)	34.27	22/4941	45/2020
DAPT	0.88 (0.34, 1.37)	16.90	19/2514	28/2531
DES LATE	0.9 (0.09, 2.74)	2.73	2/722	4/721
EXCELLENT	0.75 (0.17, 3.30)	3.02	3/512	4/510
ISAR SAFE	0.7 (0.50, 2.28)	13.62	16/1583	15/1550
ITALIC	0.9 (0.49, 1.65)	21.96	24/701	26/700
OPTIMIZE	0.73 (0.16, 3.28)	2.20	2/1099	4/1056
PRODIGY	0.66 (0.15, 2.42)	4.11	3/682	5/717
RESET	0.67 (0.51, 0.85)	100.00	80/13144	116/13263
SECURITY	0.67 (0.51, 0.85)	100.00		



■ **Kratší DA - statistick z důvodu**

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Short-Term Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Women Versus Men: A Sex-Specific Patient-Level Pooled-Analysis of Six Randomized Trials

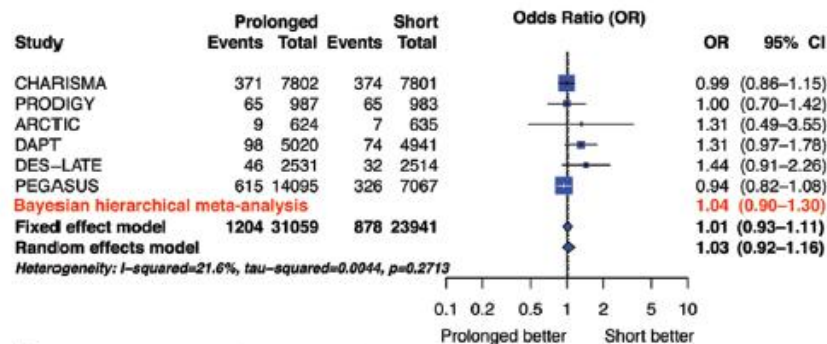
➤ DAPT na 6 měsíců je dostatečná!

- **Shrnutí: DAPT >12-30M**
 - snížení trombózy a ischemických příhod o 1-2%
 - zvýšení krvácivých komplikací o 1%
- **Na 1000 léčených nemocných:**
 - o 6 méně IM
 - o 3 méně ST
 - za cenu 5 nových závažných krvácení
(- nevýznamné – o 2 více nekardiálních úmrtí)

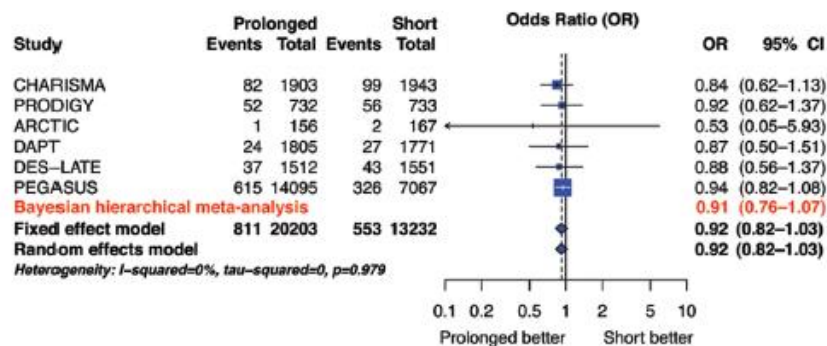
➤ DAPT na 6 měsíců je dostatečná!

All-Cause Mortality Rate in All Patients (A) and in Those With (B) and Without (C) A Prior History of Acute Coronary Syndrome

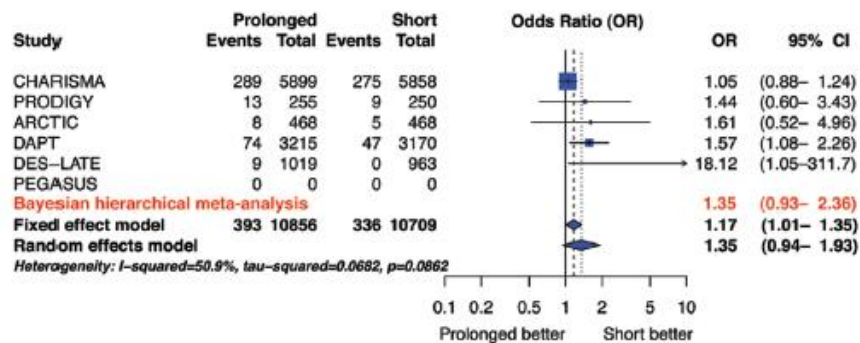
A Overall



B History of Acute Coronary Syndromes



C No History of Acute Coronary Syndrome



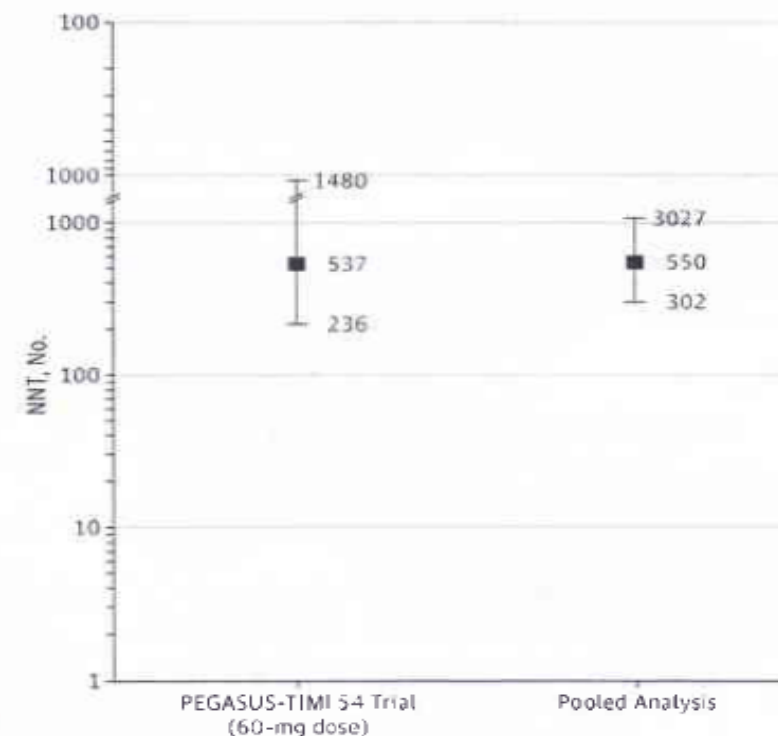
➤ DAPT na 6 měsíců je dostatečná!

Figure. Risk of All-Cause Mortality With More Intensive Prevention in Patients With Prior Myocardial Infarction

Trial	More Intensive	Less Intensive	Le	Ne
CHARRISMA (prior myocardial infarction cohort)	17/1805	17/1805	99	99
NETIC	17/1805	17/1805	56	27
DAPT MI	24/1805	24/1805	27	27
DES-LATE	37/1512	37/1512	43	43
POCUS-TIMI 54 (60-mg dose)	24/1805	24/1805	32	25
Total	773/3111	773/3111	81	81

„The successive mixing of different trials with different antiplatelet agents and different durations of follow-up not only adds clinical heterogeneity to the analysis but also unfortunately produces a perception that repetitive statistical analyses were performed to obtain a certain desired result“

Figure. Number Needed to Treat



Logarithmic plot showing the number needed to treat (NNT) for benefit or harm with each year of extended dual antiplatelet therapy in patients with prior myocardial infarction, based on analysis^{8,9} of data from the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared With Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial² and a retrospective subgroup analysis.⁴ Because the 60-mg dose of ticagrelor was associated with no significant reduction in mortality in the PEGASUS-TIMI 54 trial,² the 95% CI for the NNT crosses infinity (indicated by the break in the y-axis [//]) and includes the possibility of harm.⁹ Error bars indicate 95% CI.

(Bittle JA, Bates RE. JACC 2016, Vol 1, No 6, 62-30)

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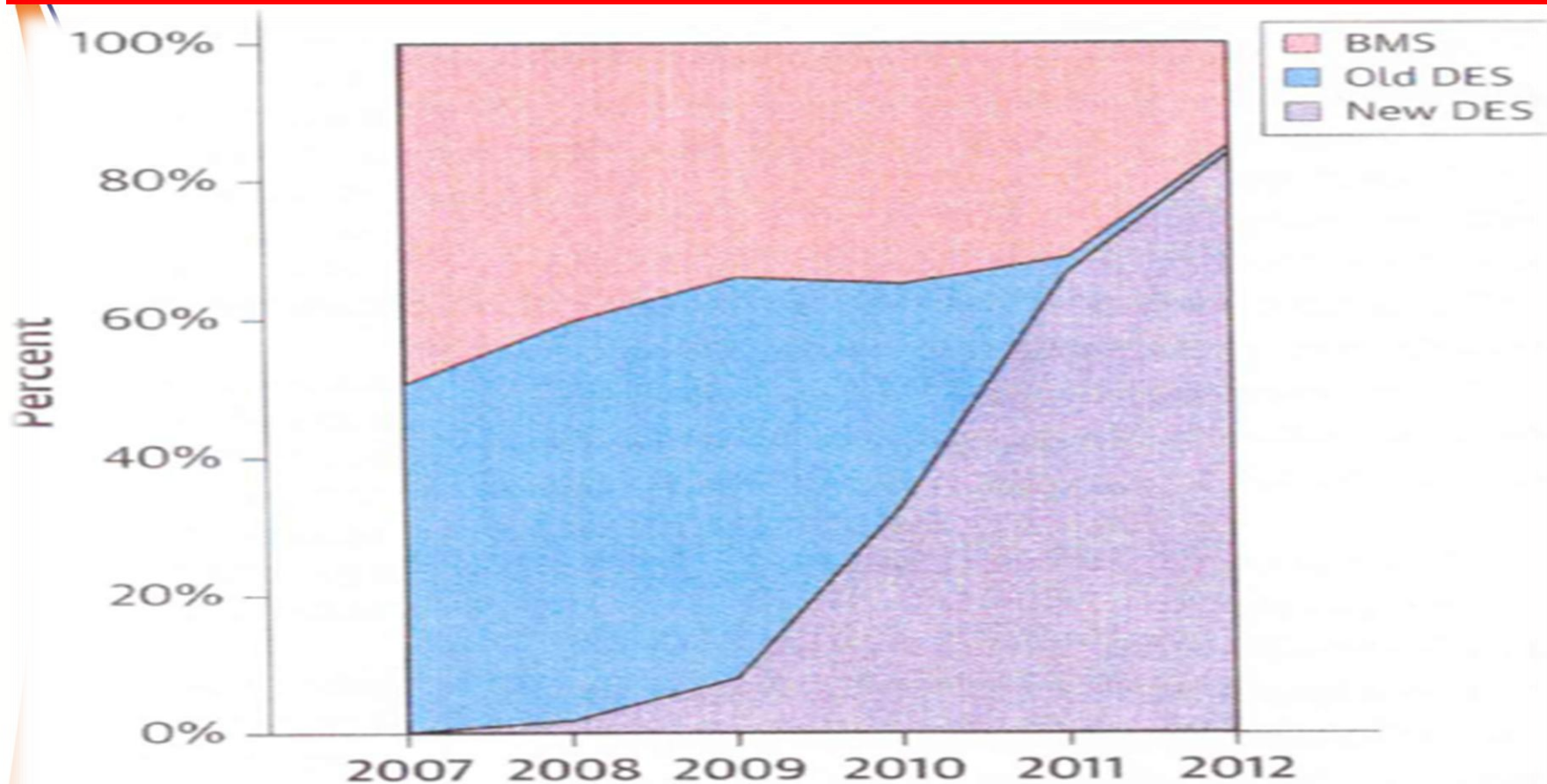


FIGURE 1 Distribution of the Use of n-DES, o-DES, and BMS During the Study Period

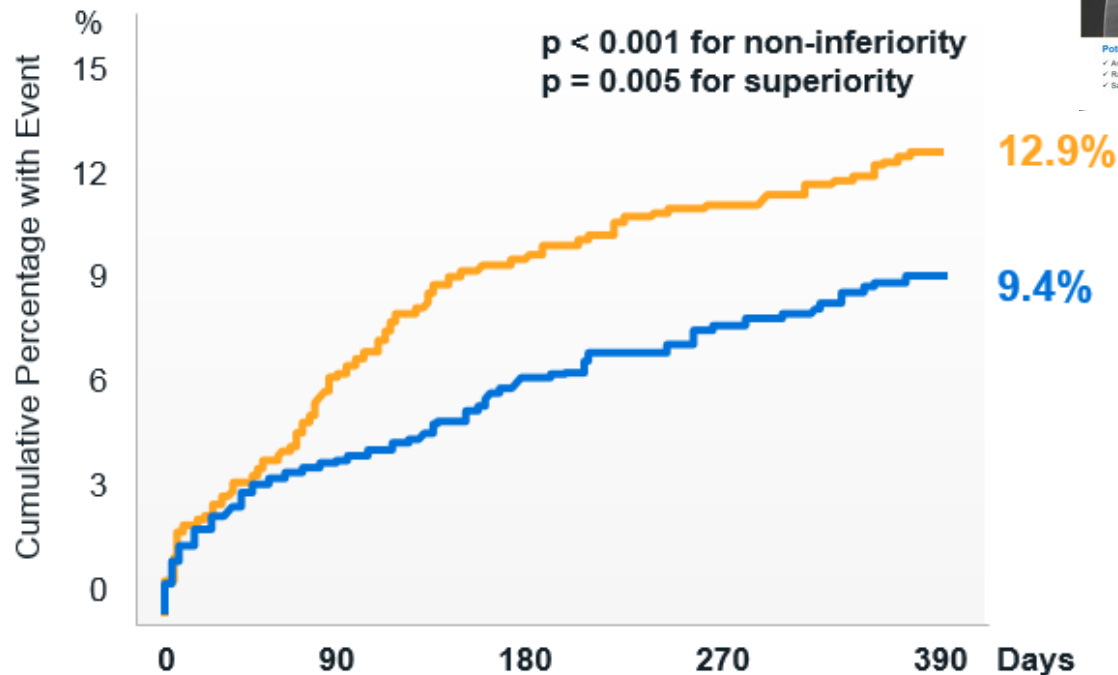
The use of new-generation drug-eluting stents (n-DES) increased from 10% in 2009 to 85% in 2012. The use of bare-metal stents (BMS) decreased from 50% in 2007 to 15% in 2012. The use of old-generation drug-eluting stents (o-DES) decreased from 50% in 2007 to 0% in 2012.

Int J Cardiol. 2015;36 (47):3320-3331



➤ DAPT na 6 měsíců je dostatečná!

Primary Safety Endpoint: 29% Reduction in the Rate of the Composite of Cardiac Death, MI, ST



Number at Risk

DCS	1221	1146	1105	1081	1045
BMS	1211	1115	1066	1037	1000

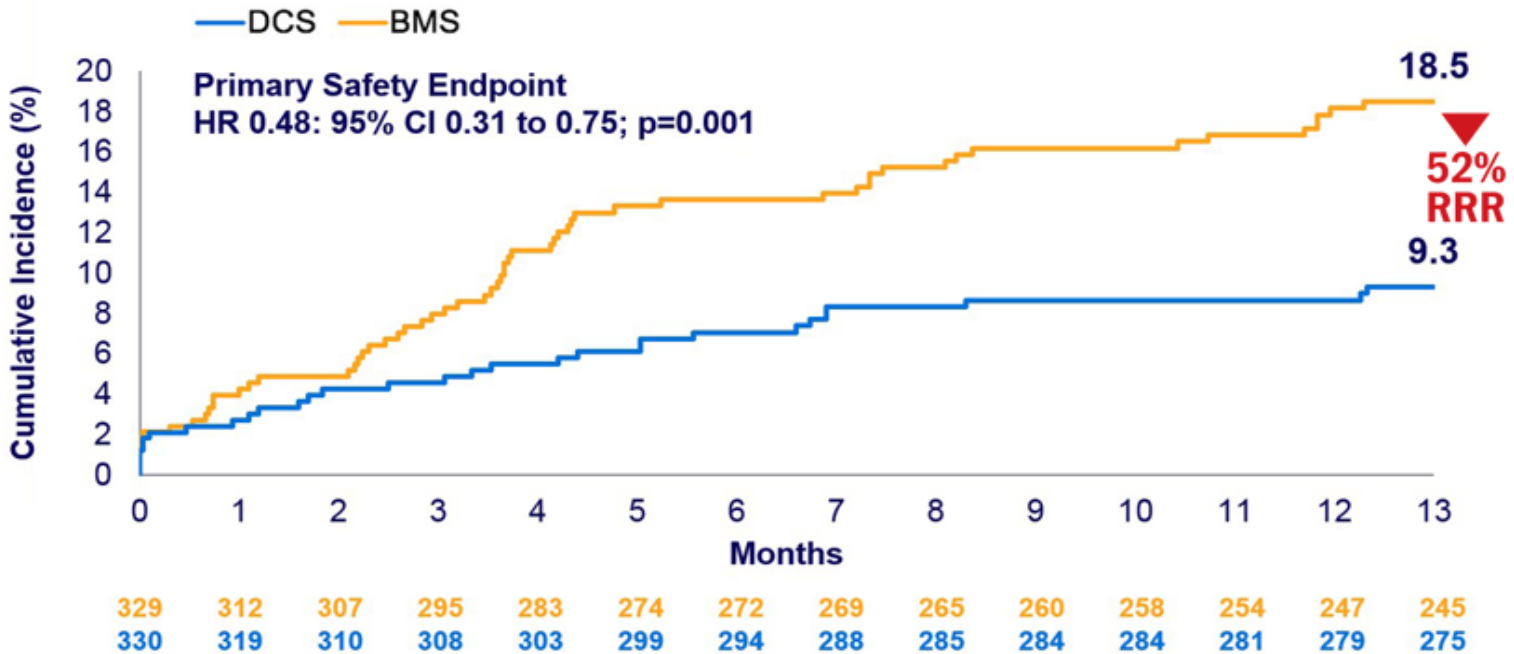
390 days chosen for assessing primary EP to capture potential events driven by the 360 day FU contact

➤ DAPT na 6 měsíců je dostatečná!

LEADERS FREE ACS

LEADERS FREE

Cardiac Death, MI, or Def / Prob ST- 12 Month FU

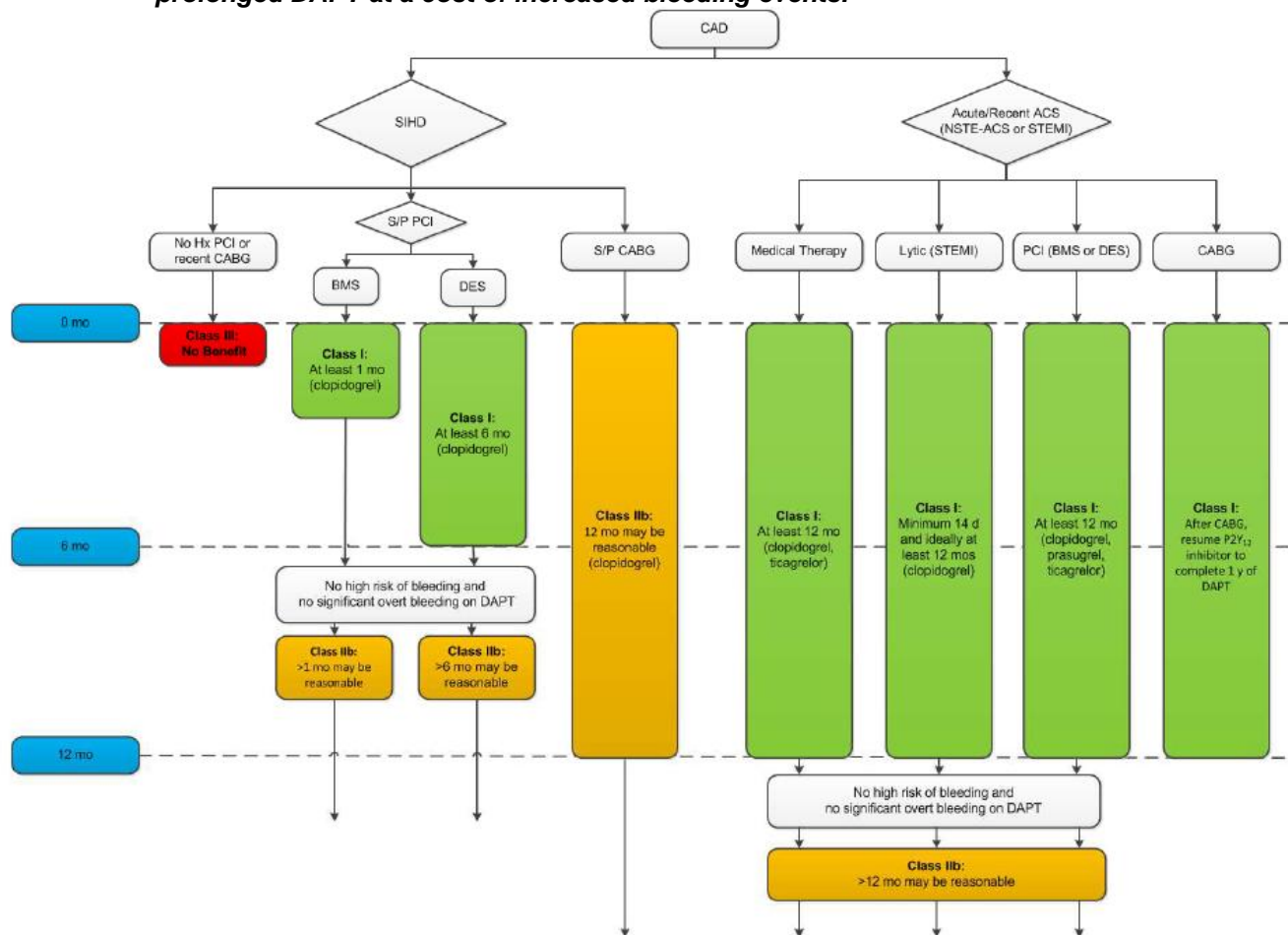


➤ DAPT na 6 měsíců je dostatečná!

CONCLUSIONS

Evidence from RCTs suggests that patients undergoing implantation of **safer, newer-generation DES** may be treated with a **minimum DAPT duration of 3 to 6 months** to prevent early and largely stent-related thrombotic events, but extension of DAPT beyond 12 months entails a tradeoff. **The declining risk of late stent thrombosis with newer-generation DES and the inability to predict life-threatening bleeding limit the appeal of 18 to 48 months of DAPT over 6 to 12 months of therapy.**

In contrast, **patients with prior MI at high risk of atherothrombosis experience fewer ischemic events with prolonged DAPT at a cost of increased bleeding events.**



➤ DAPT na 6 měsíců je dostatečná!



European Heart Journal (2014) 35, 2541–2619
doi:10.1093/eurheartj/ehu278

ESC/EACTS GUIDELINES



2014 ESC/EACTS Guidelines on myocardial revascularization

DAPT treatment according to Bleeding Risk status

	SCAD		ACS	
	BMS	DES	BMS	DES
Low Bleeding Risk	1 M	6 M	12 M	12 M
High Bleeding Risk	1 M	< 6 M (option)	<12M (option)	<12 M (option)

In SCAD, recommendation is IA for BMS, IB for DES in LBR patients and IIBA for DES in HBR patients.
In ACS, recommendation is IA for 12 months for LBR, but there is no specific recommendation for HBR patients.

➤ DAPT na 6 měsíců je dostatečná!

☐ Závěry:

- *Současná data nesvědčí pro > 12 M DAPT*
(Na 1000 léčených nemocných: o 6 méně IM, o 3 méně ST, o 5 více závažných krvácení;
/+ možná o 2 více úmrtí/)
- *S novými typy DES klesá ST/IM, krvácení má vyšší mortalitu než pozdní trombóza stentu, ekonomické aspekty.*
- *Individualizovaná DAPT na základě zhodnocení individuálního ischemického/krvácivého rizika a přání nemocného*
- *Nové studie DAPT vs monoterapie*
(GLOBAL LEADERS, TWILIGHT study)

KZ

➤ DAPT na 6 měsíců je dostatečná!

